Do We Need an Implantable Cardioverter-defibrillator for Primary Prevention in Cardiac Resynchronisation Therapy Patients

Katritsis, Demosthenes G ; Auricchio, Angelo

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Do We Need an Implantable Cardioverter-defibrillator for Primary Prevention in Cardiac Resynchronisation Therapy Patients?

Demosthenes G Katritsis[1] and Angelo Auricchio[2]

1. Hygeia Hospital, Athens, Greece; 2. Fondazione Cardiocentro Ticino, Lugano, Switzerland

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Correspondence: Demosthenes G Katritsis, Hygeia Hospital, Erithrou Stavrous 4, Athens 15123, Greece. E: dkatrits@dgkatritsis.gr

Despite the fact that more than 20 years have passed since the clinical introduction of cardiac resynchronisation therapy (CRT), one of the key questions – do we need an ICD for primary prevention of sudden cardiac death (SCD) in CRT patients? – is still unanswered.

Prospective Randomised Controlled Trials

Multiple prospective randomised controlled trials have been conducted to establish the use of CRT in different categories of heart failure patients; these studies have consistently demonstrated the superiority of CRT compared with best medical therapy in improving ventricular function, the patient's functional capacity, and prognosis. The greatest majority of prospective randomised controlled studies used a CRT device combined with an ICD (CRT-D).

Indeed, past prospective randomised controlled trials of primary prevention in patients with heart failure indicated that ICD reduced mortality in post-MI patients with left ventricular ejection fraction (LVEF) <30 % (Multicentre Automatic Defibrillator Implantation Trial II; MADIT II),[1] and ischaemic or non-ischaemic cardiomyopathy in patients with LVEF <35 % (Sudden Cardiac Death in Heart Failure Trial; SCD-HeFT).[2]

In patients with LVEF <35 %, advanced heart failure (New York Heart Association; NYHA class III or IV) due to ischaemic or non-ischaemic cardiomyopathies and a QRS interval >120 ms, the presence of ICD capabilities reduced mortality (Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure trial; COMPANION).[3] Of note, the addition of CRT to patients who already require an ICD also reduces mortality.

In the Resynchronisation–Defibrillation for Ambulatory Heart Failure Trial (RAFT) in patients with NYHA II or III heart failure, LEVF ≤30 %, and a QRS ≥120 ms or paced QRS ≥200 ms, the addition of CRT to an ICD improved survival, albeit at a cost of increased implantation-related complications (RAFT).[4] In the MADIT with Cardiac Synchronisation Therapy (MADIT-CRT), in patients with ischaemic (NYHA I or II) or non-ischaemic (NYHA II) cardiomyopathy, LVEF ≤30 %, and QRS≥ 130 ms with left bundle branch block morphology, CRT offered a 11 % reduction in mortality compared with an ICD alone.[5] In a real-world retrospective cohort study using National Cardiovascular Registry data linked with Medicare claims, patients who were eligible for CRT-D according to established criteria and who received CRT-D had significantly lower risks for death and readmission than those who received an ICD therapy alone.[6]

Clinical Daily Practice

All that, however, contrasts with clinical daily practice in which approximately one-third of patients receive a CRT without an ICD function (CRT-P). The clinical justification to offer a sizable group of patients a CRT-P device is given by the lack of a perceived realistic, additional survival benefit, as provided by an ICD, in addition to what may be achieved by CRT-P alone. Clinical factors possibly associated with higher mortality due to heart failure rather than SCD (the latter can be effectively reduced only by an ICD) are advanced age, cardiovascular comorbidities, some neurological diseases associated with severe cognitive and/or physical impairment, psychiatric disorders, and life expectancy <1 year due to neoplasia.

Another key factor that may justify the use of CRT-P instead of CRT-D could be represented by the aetiology, as occurs with non-ischaemic cardiomyopathy (NICM). Both the Cardiomyopathy Trial (CAT)[7] and Amiodarone Versus Implantable Cardioverter-Defibrillator Trial (AMIOVIRT)[8] used single- and dual-chamber ICDs, but neither trial showed any survival benefit of ICDs in patients with NICM. Importantly, these studies involved small numbers of patients.

In the Defibrillators in Non-Ischaemic Cardiomyopathy Treatment Evaluation (DEFINITE) study, in which 458 patients with NICM were randomised to medical therapy or an ICD, ICD therapy did not reduce total mortality, despite a significant reduction in SCD.[9] In the recent Defibrillator Implantation in Patients With Non-ischaemic Systolic Heart Failure (DANISH) study, neither ICD nor CRT-D reduced total mortality in patients with NICM.[10] Notably, only patients aged younger than 68 years had a significant reduction of SCD and overall mortality by CRT-D compared with CRT-P/best medical therapy. These studies cast doubt on the relative benefit of CRT-D versus CRT-P in patients with NICM, despite the promising results in favour of ICD in the non-ischaemic setting by a recent meta-analysis.[11]

New Developments

Some recent data by Leyva et al., who evaluated mid-wall cardiac fibrosis by cardiac magnetic resonance, showed that CRT-D was markedly superior to CRT-P in terms of total mortality, cardiovascular mortality, and all composite endpoints in those patients with mid-wall fibrosis, whereas no benefit from CRT-D over CRT-P was observed in those patients without mid-wall fibrosis with respect to any of the endpoints.[12] These findings indirectly substantiate the results of a meta-analysis by Disertori et al. indicating that late gadolinium enhancement by cardiac magnetic resonance is a powerful predictor of ventricular arrhythmic risk in patients with ventricular dysfunction, irrespective of aetiology.[13] The prognostic power of late gadolinium enhancement is particularly strong in patients with severely depressed ejection fraction, which suggests its potential to improve patient selection for ICD implantation. However, to be put into practice, late gadolinium enhancement protocols need to be standardised with respect to execution modalities and the setting of diagnostic thresholds.

New developments may also provide additional data and new insights. The value of electrophysiology testing in assessing the need for an ICD, at least in the ischaemic setting, continues to be debated.[14] Such a possibility could further facilitate the selection of appropriate CRT-D candidates.

Recent studies using His bundle pacing could further revolutionise the field of CRT. In some cases, a significant improvement of functional capacity and ventricular function has been observed.[15–17]

Whether and in which patients His bundle pacing may represent a suitable alternative to CRT remains to be determined. Similarly, whether improvement of the efficacy of CRT will be adequate to refute the need for an ICD in certain patients remains to be seen.

Conclusion

Currently, and in the absence of hard data to guide clinical practice in this respect, we have to rely on the recommendations by the 2013 (and 2017) update of the American College of Cardiology/American Heart Association and 2016 European Society of Cardiology guidelines on heart failure, and recommend an ICD, with or without CRT, in patients with non-ischaemic or ischaemic (at least 40 days post-MI) heart failure, LVEF ≤35 %, and NYHA II/III.[18,19] ■

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